Amendments to the Drawings:

Replacement drawings are included in the Attachment. The attached sheets of replacement drawings include changes to FIG. 11. These sheets replaces the original sheets that include FIG. 1 through FIG. 14. In FIG. 11, an obvious typographical error is corrected, basis for which can be found throughout the specification (for example, see page 9, lines 18-19). FIGS. 1-10 and 12-14 were redrawn to improve visual clarity but no changes have been made.

Please forward the approved drawings to the Drawing Branch.

Attachment: Replacement Sheets 1-13
Annotated Sheet 10 Showing Changes Made to FIGURE 11.

REMARKS

A check in the amount of $475 for the fee for a three-month extension is included with this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 70, 72-79, 92-94, 123-124, 127-133 and 135-138 are pending in this application. Claim 134 is cancelled herein without prejudice or disclaimer. The specification is amended to correct minor typographical errors. The paragraph on page 46 is amended to correct the reference to FIG. 9 on line 27 to properly refer to FIG. 10, since FIG. 10 shows extension of a nucleic acid probe by ligation. Basis for the amendment is found throughout the specification (for example, see page 9, lines 15-19). The paragraph on page 47 is amended to correct the reference to Example 4 on line 18 to properly refer to Example 5, which exemplifies DNA ligation to oligonucleotide arrays. Basis for the amendment is found throughout the specification (for example, see page 35, line 1 through page 38, line 27). FIGURE 11 is amended to correct an obvious typographical error, basis for which can be found throughout the specification (for example, page 9, lines 18-19).

Claim 70 is amended herein to remove the references to the 3'-terminus and 5'-terminus. Basis for the amendment is found throughout the application (for example, see page 20, lines 14-17). Claim 70 is also amended to include the recitation that the variable nucleotide sequence is not at a terminus. The instant specification teaches methods to create an array of probes that include a variable sequence that is not terminal in the single-stranded region (for example, see page 27, lines 6-25). The amendment is not meant to be one in which a critical limitation is added, rather it is meant as an indication of what <u>not</u> is being claimed. The ability to carve out what is patentable is well recognized.

> Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable. As we said in a different context ... [t]o rule otherwise would let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed. *In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A 1976).

Thus, claim 70 as amended was within the possession of the inventor at the time of filing the application and the amendment is presented as a means of carving out what is and what is not covered by the claim. No new matter is added.

Claims 70 and 127 are amended to replace the recitation "random nucleotide sequence" with the recitation "variable nucleotide sequence." Basis for the amendment is found throughout the specification (for example, see page 30, lines 4-7; page 31, lines 4-8 and lines 13-15; page 34, lines 10-19).

Claim 74 is amended herein to more distinctly claim the subject matter. Basis for the amendment can be found throughout the specification (for example, see page 26, lines 14-28 and page 21, lines 1-8). Claim 75 is amended to include the recitation "which is fixed to a solid support" necessitated by the amendment of claim 74 herein. Basis for the amendment is found throughout the specification (for example, see page 26, line 29).

Claim 123 is amended to include the recitation "the probes are fixed to a solid support by conjugating to a coupling agent." Basis for the amendment can be found throughout the specification (for example, see page 13, lines 19-24). Claim 124 is amended to include the recitation "wherein the variable region is of length n and the array comprises" and to replace the recitation "4^R" with "4^n" necessitated by the amendment of claim 74 herein. Basis for the amendment can be found throughout the specification (for example, see page 44, lines 1 and 25).

Claim 127 is amended to more distinctly claim the subject matter. Basis for the amendment can be found throughout the specification (for example, see page 12, lines 1-6 and Macevics, WO 90/04652, page 3, line 30 through page 4, line 25, which is equivalent to U.S. 5,002,867, col. 2, line 58 through col. 3, line 23, incorporated by reference in the instant specification and provided with a previous Information Disclosure Statement). Claim 128 is amended to correct the dependency of the claim. Claim 135 is amended to change the dependency of the claim and to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (for example, see page 49, lines 20-23, and see Macevics, WO 90/04652, page 4, line 12 through page 5, line 1 and page 8, line 7 through page 9, line 18 or U.S. 5,002,867, col.3, line 23-47 and col. 6, line 39 through page 7, line 23).

Claims 136-139 are added herein. Basis for claim 136 can be found throughout the specification (for example, see page 26, lines 27-28). Basis for claim 137 can be found throughout the specification (for example, see page 8, line 5-7). Basis for claim 138 can be found throughout the specification (for example, see page 13, lines 19-24).

Therefore, no new matter is added nor are any amendments made to change the scope of the claims. The amendments should place the claims and the application into condition for allowance.

OBJECTION TO THE AMENDMENT FILED 25 APRIL 2003 UNDER 35 U.S.C. § 132

The Amendment, filed 25 April 2003, is objected to under 35 U.S.C. §132, because it allegedly introduces new matter into the disclosure because of the recitation "degenerate single-stranded portion" in claim 70 and the recitation "adjacent sequence" in claim 74.

While not conceding the propriety of this rejection, it is respectfully submitted that this rejection is obviated by the amendment of claims 70 and 74 herein. The recitations to which the objections are raised are deleted from claims 70 and 74.

REJECTION OF CLAIMS 70, 72-79, 92-94, 123, 124, 134 AND 135 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 70, 72-79, 92-94, 123, 124, 134 and 135 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner alleges that the specification does not provide adequate support for the recitation "a degenerate single-stranded portion" in claim 70 or the recitation "adjacent sequence" in claim 74.

While not conceding the propriety of this rejection, the amendment of claims 70 and 74 herein renders the rejection moot.

REJECTION OF CLAIMS 74-76, 92-94, 123, 124, 127-132, 134 AND 135 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 74-76, 92-94, 123, 124, 127-132, 134 and 125 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

CLAIM 74

The Examiner alleges that it is unclear whether the "adjacent sequence" recited in claim 74 is hybridized to the single-stranded portion or whether the "adjacent sequence" is adjacent to the probe on the array.

Applicant respectfully submits that amendment of claim 74 herein renders the rejection moot.

CLAIM 127

The Examiner alleges that it is unclear whether the recitation "that base" in claim 127, line 6 refers to the "one base" recited in line 5.

Applicant respectfully submits that amendment of claim 127 herein to recite "a selected base" in line 5 and "the selected base" in line 6 obviates this rejection.

CLAIM 134

The Examiner alleges that claim 134 is indefinite because it is unclear how the recitation "gapped" limits a segment in claim 134.

While not conceding the propriety of this rejection, it is respectfully submitted that this rejection is rendered moot with respect to claim 134, which is cancelled herein without prejudice.

THE REJECTION OF CLAIMS 70 AND 72 UNDER 35 U.S.C. § 102(e)

Claims 70 and 72 are rejected under 35 U.S.C. § 102(e) as anticipated by Deugau *et al.* (U.S. Patent No. 5,508,169) because Deugau *et al.* allegedly discloses an array of nucleic acid probes having a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus (Fig. 2; column 11, lines 14-25; and column 9, lines 28-42).

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 70 is directed to an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a variable nucleotide sequence within the single-stranded portion, where the variable sequence is not at the terminus. Claims 72 and 73 depend from claim 70 and are directed to various embodiments thereof.

Disclosure of Deugau *et al.*

Deugau *et al.* discloses indexing linkers that have single-stranded portions on both ends or on only one end. The reference discloses that the double-stranded portion can be at either the 3'-terminus or at the 5'-terminus. Deugau *et al.* discloses that the indexing linkers have a protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and that neither single-stranded end will function as a restriction endonuclease recognition site. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each end of a fragment (col. 7, lines 48-60).

Differences between the claimed subject matter and the disclosure of Deugau *et al.*

Deugau *et al.* does not disclose a probe that includes a variable nucleotide sequence that is not at the terminus of the single-stranded portion. The Examiner alleges that claim 33 of Deugau *et al.* discloses the array of instant claim 70. Claim 33 of Deugau *et al.* states

> 33. In a polymerase chain reaction kit comprising: heat source, oligonucleotide primers, DNA polymerase and a mixture of all four deoxynucleotide precursors, wherein the improvement comprises:
>
> a panel for obtaining indexed DNA fragments from a mixture of DNA fragments, for identifying, isolating, mapping, amplifying, or sequencing said fragments,
>
> said panel comprising a set of indexing linkers, each said indexing linker being a DNA duplex having one 3'- or 5'-protruding single strand of a length corresponding to the 3'- or 5'-protruding single strand of the cleavage site of a Type IIS restriction endonuclease or a restriction endonuclease recognizing interrupted palindromic sequences, wherein said set comprises a collection of

> indexing linkers whose 3'- or 5'-protruding single strands collectively encode up to all possible permutations and combinations of the nucleotides, A, C, G and T, and wherein said indexing linkers are physically separated from each other on the basis of the identity of their 3'- or 5'-protruding single strand.

Applicant respectfully submits that claim 33 does not disclose an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion, and a variable nucleotide sequence within the single-stranded portion that is not at the terminus of the single-stranded region.

The Examiner alleges that the protruding single strand of Deugau *et al.* is the same as the instantly claimed "variable sequence" and that Figure 2 illustrates a set of indexing linkers as instantly claimed. Figure 2 of Deugau *et al.* illustrates a set of probes that have variable sequences at the **terminus** of the probes. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce protruding overhangs on each **end** of a fragment (col. 7, lines 48-60). Thus, because the restriction endonucleases produce terminal overhangs, and the Examiner alleges that the overhangs are the "variable sequence" as instantly claimed, the index linkers of Deugau *et al.* do not include a variable sequence that is not terminal. Hence, Deugau *et al.* does not disclose every element of the claimed subject matter of claims 70 and 72. Therefore, because Deugau *et al.* does not disclose all elements of the claimed subject matter, Deugau *et al.* does not anticipate claims 70 and 72.

REJECTION OF CLAIM 73 UNDER 35 U.S.C. §103(a)

Claim 73 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Brenner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1989, 86:8902-8906) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except the specific means by which the probes are immobilized, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches that biotin/streptavidin provides a versatile means of capture immobilization.

This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp*. 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

CLAIM 73

Claim 73 depends from claim 70 and is directed to an embodiment where the probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Differences Between the Claims and the Teachings of the Cited References

Deugau *et al.*

See related section above.

Brenner *et al.*

Brenner *et al.* teaches a fluorescent DNA sampled sequence fingerprinting procedure that couples band separation with sampled nucleotide sequencing (page 8902, right column, lines 11-14). The reference teaches cleaving DNA using endonuclease followed by electrophoresis and analysis by fluorescent emissions (paragraph bridging pages 8902-8903). Brenner *et al.* teaches that following specific cleavage using any restriction enzyme, biotin can be attached to each primary cleavage end by adding biotinylated nucleotides (page 8904, left column, second full paragraph).

Brenner *et al.* does not teach or suggest an array of nucleic acid probes, or an array of probes where each probe has a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

As discussed above in the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of nucleic acid probes having a variable sequence within the single-stranded portion that is not at the terminus. Brenner *et al.* does not cure this defect.

Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* does not teach or suggest a probe having a double-stranded region, a terminal single-stranded region and a variable sequence within the single-stranded region that is not at

the terminus. As shown in Figure 4, after specific cleavage, all of the resulting fragments have a single-stranded region on both ends (page 8904). Brenner *et al.* does not teach or suggest including a non-terminal variable sequence within the single-stranded region. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 73.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded region and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed arrays of claim 73. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REJECTION OF CLAIMS 74-79, 92-94, 124 AND 129-135 UNDER 35 U.S.C. §103(a)

Claims 74-79, 92-94, 124 and 129-135 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Ghosh *et al.* (*J. Chem Inf. Comput. Sci.* 38: 1161-70 (1998)) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except conjugation of the probe to the support through a coupling agent, but Ghosh *et al.* allegedly cures this defect.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Independent claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid and a longer single-stranded second nucleic acid having a variable terminal nucleotide sequence ligated to an oligonucleotide that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion.

Claims 77-79 depend from claim 70, and are directed to various embodiments of claim 70, which is directed to an array of nucleic acid probes, where each probe has a double-stranded portion, a terminal single-stranded portion, and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Independent Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions; and the array is divided into subarrays, where for each subarray a selected base of the nucleotide sequence occupies the fixed positions of the probes and all other bases except the selected base are used in the non-fixed positions such that the fixed positions of the different subarrays are occupied by a different selected base; and the probes are fixed to a solid support by conjugating to a coupling agent. Claims 129-135 depend from claim 127 and are directed to various embodiments thereof.

Differences Between the Claims and the Teachings of the Cited References

Deugau *et al.*

See related section above. In addition, Deugau *et al.* does not teach or suggest a single-stranded portion of a probe that includes a predetermined sequence of fixed and non-fixed positions. Deugau *et al.* does not teach or suggest dividing its array of indexing linkers into subarrays.

Ghosh *et al.*

Ghosh *et al.* teaches the direct covalent attachment of DNA to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities. Ghosh *et al.* teaches a number of chemical methods for the attachment of DNA to solid supports through stable covalent linkages, including carbodiimide-mediated end attachment or phosphodiester bonds (page 5354). DNA oligonucleotides are covalently attached to the solid supports by conversion to phosphoramidate derivatives that react with amino or carboxyl functionalities on the support surface (pages 5359-60 and 5369).

Ghosh *et al.* does not teach or suggest any other method of attaching oligonucleotides to a solid support other than direct covalent attachment of the nucleotide to reactive functionalities on the substrate surface such as aminohexyl and cystaminyl functional groups. Ghosh *et al.* does not teach or suggest an oligonucleotide having a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* does not teach or suggest a single-stranded portion of a probe that includes a predetermined sequence of fixed and non-fixed positions. Ghosh *et al.* does not teach or suggest dividing an array of nucleic acid probes into subarrays where within each subarray a selected base occupies the fixed positions and all other bases except the selected base occupy the non-fixed positions in the single-stranded portion. Ghosh *et al.* does not teach or suggest covalent attachment of ribonucleic acid or protein nucleic acid to solid supports.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Ghosh *et al.* does not result in the instantly claimed arrays.

Claims 77-79

Claims 77-79 depend from claim 70 and are directed to embodiments of an array of probes each of which contains a double-stranded portion, a terminal

single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. The arrays of claims 77 and 78 include probes labeled with a detectable label. Claim 79 is directed to an array where the nucleic acids are DNA, RNA, PNA, or a combination thereof. As discussed above, Deugau *et al.* does not teach or suggest an array of probes each of which includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of nucleic probes, nor does Ghosh *et al.* teach or suggest a probe that includes a double-stranded portion, a terminal single-stranded and a variable nucleotide sequence within the single-stranded portion that is not at the terminus. Ghosh *et al.* provides limited information on the oligonucleotides used, teaching their length (page 5353 and page 5363) and methods of derivatizing the oligonucleotides (page 5358). Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of oligonucleotides to a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claims 77-79.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a double-stranded portion, a terminal single-stranded portion and a variable nucleotide sequence within the single-stranded portion that is not at the terminus.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed arrays of claims 77-79. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 74-76, 92-94, 124 and 135

Deugau *et al.* does not teach or suggest an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25

and a longer single-stranded second nucleic acid of about 20-30 nucleotides having a variable terminal nucleotide sequence of between about 3-10 nucleotides ligated to an oligonucleotide of about 4-20 nucleotides that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion.

As discussed above, Deugau *et al.* teaches that its indexing linkers are terminated by overhangs produced by cleavage with restriction endonucleases and are of a length of 3, 4, or 5 nucleotides. Deugau *et al.* does not teach or suggest an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region that includes the variable sequence is greater than 5 nucleotides.

Ghosh *et al.* does not cure this defect. As discussed above, Ghosh *et al.* teaches a method of immobilizing DNA to a solid support, but Ghosh *et al.* does not teach or suggest an array of nucleic acid probes, nor a probe that includes a double-stranded portion at one terminus and a single-stranded portion at the other terminus. Ghosh *et al.* does not teach or suggest a single-stranded portion that includes a variable nucleotide sequence between about 3-10 nucleotides in length and an oligonucleotide of about 4-20 nucleotides in length. Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of DNA to a solid support, the combination of the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 74 and its dependant claims.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where the single-stranded portion includes a variable nucleotide sequence between about 3-10 nucleotides in length and an oligonucleotide of about 4-20 nucleotides in length. Thus, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed array of claim 74 and its dependent claims. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 127 and 129-134

Deugau *et al.* discloses that its comprehensive panel of indexing linkers contains all possible combinations and permutations of the nucleotides A, C, G and T. Deugau *et al.* does not teach or suggest an array of nucleic acid probes where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed positions. Deugau *et al.* does not teach or suggest an array where within the array the probes are divided into subarrays; and in each subset, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* does not teach or suggest an array of nucleic acid probes where the probes have a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, where the single-stranded portion of each probe includes a predetermined sequence of fixed and non-fixed position. Ghosh *et al.* does not teach or suggest dividing an array of probes into subarrays. Ghosh *et al.* does not teach or suggest selecting a base of the nucleic acid to occupy the fixed positions and using all other bases except the selected base in the non-fixed positions.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed array of claim 127 and its dependent claims. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 123 AND 128 UNDER 35 U.S.C. §103(a)

Claims 123 and 126 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deugau *et al.* in view of Ghosh *et al.* and further in view of Brenner *et al.* (Proc. Natl. Acad. Sci. USA, 1989, 86:8902-8906) because the combination of Deugau *et al.* and Ghosh *et al.* allegedly teaches all elements of the claimed subject matter except the use of the coupling agents as instantly claimed, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches biotin/streptavidin as a means of immobilization.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 123 depends from claim 74, and claim 128 depends from claim 127. Both claims are directed to an embodiment where the probes are fixed to a solid support through a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Differences Between the Claims and the Teachings of the Cited References

Deugau *et al.*

See related section above.

Ghosh *et al.*

See related section above.

Brenner *et al.*

See related section above.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* and Ghosh *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

Claim 123

As discussed above in the previous § 103(a) rejection directed to claim 74 and its dependents, neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of probes where each probe includes a double-stranded portion and a terminal single-stranded portion, where the single-stranded portion includes a variable nucleotide sequence between about 3-10 nucleotides and an oligonucleotide of about 4-20 nucleotides in length.

Brenner *et al.* does not cure this defect. Brenner *et al.* teaches capture fingerprinting analysis of DNA. Brenner *et al.* does not teach or suggest an array of nucleic acid probes, or an array of probes having a double-stranded portion and a single-stranded portion, where the single-stranded portion includes a variable nucleotide sequence between about 3-10 nucleotides in length and an oligonucleotide of about 4-20 nucleotides in length. Hence, even if, arguendo, Brenner *et al.* teaches coupling DNA oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Ghosh *et al.* and Brenner *et al.* does not teach or suggest every element of claim 123.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 123. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claim 128

As discussed above in the traverse of the rejection directed to claim 127, neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where the array is divided into subarrays; or a probe having a single-stranded region that includes a predetermined sequence of fixed and non-fixed positions; or a subarray, where within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions.

Brenner *et al.* does not cure this defect. Brenner *et al.* does not teach or suggest dividing an array of nucleic acid probes into subarrays, or that the single-stranded portion of each probe include a predetermined sequence of fixed and non-fixed positions. Brenner *et al.* does not teach or suggest a single-stranded portion of a probe where a selected base of the nucleic acid occupies the fixed positions and all other bases except the selected base are used in the non-fixed positions. Hence, even if, arguendo, Brenner *et al.* teaches coupling

DNA oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.*, Ghosh *et al.* and Brenner *et al.* does not teach or suggest every element of claim 128.

None of Deugau *et al.*, Ghosh *et al.*, nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where the array the probes is divided into subarrays, where in each subarray, within the single-stranded portion of each probe, a selected base of the nucleic acid occupies the fixed positions of the probes and all other bases except the selected base are used in the remaining positions.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 128. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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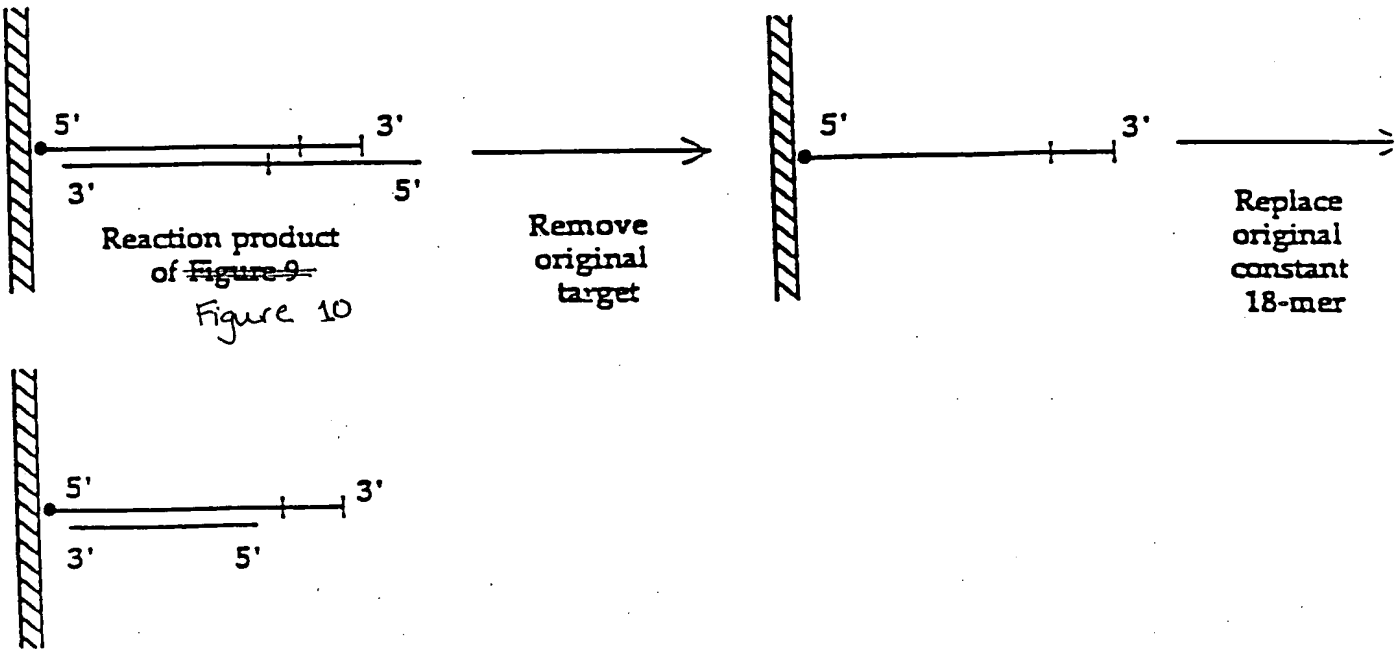

Preparation of a customized probe containing a 10 bp sequence present in the original target DNA

FIGURE 11